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Health Effects Assessment for 1,2,4-Trichlorobenzene

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HEALTH EFFECTS ASSESSMENT FOR 1,2,4-TRICHLOROBENZENE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 1,2,4-trichlorobenzene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to June, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Chlorinated Benzenes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-028. NTIS PB81-117392.

U.S. EPA. 1980b. Hazard Profile for 1,2,4-Trichlorobenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1983a. Reportable Quantity Document for 1,2,4-Trichlorobenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985a. Health Assessment Document for Chlorinated Benzenes. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-015F. NTIS PB85-150332.

U.S. EPA. 1985. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for 1,2,4-Trichlorobenzene. Online (verification date 2/26/86). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

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Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980c) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980c). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

An RfD_{SO} of 14 mg/day and an RfD_O of 1.4 mg/day were calculated for 1,2,4-trichlorobenzene based on a NOAEL of 20 mg/kg/day from a 90-day gavage study in male rats (Carlson and Tardiff, 1976). Altered enzyme activities were observed at all treatment levels but increased relative liver weight was observed only at 40 mg/kg/day, the highest dose tested. The U.S. EPA (1986) also derived an RfD of 1.4 mg/day on the same basis. A CS of 12.4 was calculated for oral exposure to 1,2,4-trichlorobenzene (U.S. EPA, 1983a) based on increased adrenal weights in rats in a multigeneration reproduction study (Robinson et al., 1981).

An RfD_{SI} of 1.75 mg/day and RfD_I of 0.18 mg/day were calculated from a NOAEL in rats exposed to 3 ppm (22 mg/m^3) for 3 months (Watanabe et al., 1978). Increased urinary uroporphyrin was noted at 10 ppm.

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The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and John Helms (Office of Toxic Substances) was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
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LIST OF ABBREVIATIONS

CS	Composite score
EPN	O-ethyl O-para-nitrophenyl phenylphosphorothioate
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
PfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of 1,2,4-trichlorobenzene are presented in Table 1-1.

In the atmosphere, 1,2,4-trichlorobenzene is expected to exist primarily in the vapor phase and would be subject to removal by reaction with photochemically generated HO radical. Based on an observed reaction rate constant of 0.532×10^{-12} cm^3/molecule-sec at 23°C (Atkinson, 1985) and an ambient HO radical concentration of 8.0×10^5 molecule/sec. The hydroxyl reaction half-life is ~18.8 days.

In water, 1,2,4-trichlorobenzene should adsorb to suspended solids and sediments and may bioaccumulate in some aquatic organisms. Significant volatilization from water is expected, since a volatilization half-life of 11-22 days was determined during mesocosm experiments with aerated seawater (Wakeham et al., 1983); a volatilization half-life of 6.9 hours was estimated for a river 1 m deep flowing at 1 m/sec with a windspeed of 3 m/sec, based on the method of Lyman et al. (1982). The overall aquatic half-lives for 1,2,4-trichlorobenzene in rivers, lakes and groundwater were estimated to be 0.3-3, 3-30 and 30-300 days, respectively (Zoeteman et al., 1980).

In soil, 1,2,4-trichlorobenzene is expected to remain strongly sorbed and therefore will not leach appreciably into the groundwater; however, 1,2,4-trichlorobenzene has been detected in some groundwater samples which indicates that it can be transported in soils under certain conditions. A biodegradation study (Marinucci and Bartha, 1979) suggests that this compound may biodegrade slowly in aerobic soil, but it is not expected to biodegrade in groundwater (Roberts et al., 1980).

TABLE 1-1

Selected Chemical and Physical Properties and Environmental Fate of 1,2,4-Trichlorobenzene

Property		Reference
CAS number:	120-82-1	
Chemical class:	haloaromatic compound	
Molecular weight:	181.46	
Vapor pressure:	0.45 mm Hg at 25°C	Mackay and Shui, 1981
Water solubility:	25-35 mg/ℓ at 25°C	Mackay and Shui, 1981
Log octanol/water partition coefficient:	4.12	Hansch and Leo, 1986
Bioconcentration factor:	1200-3200, rainbow trout (*Salmo gairdneri*)	Oliver and Niimi, 1983
	2800, fathead minnow (*Pimephales promelas*)	Veith et al., 1979
	182-815, bluegill sunfish (*Lepomis macrochirus*)	Barrows et al., 1980; U.S. EPA, 1980a
Soil adsorption coefficient:	~1000-5000	Friesel and Steiner, 1984; Chiou et al., 1983; Wilson et al., 1981; U.S. EPA, 1985a
Half-lives in		
Air:	~19 days (estimated)	Atkinson, 1985
Surface Water:	0.3-30 days (estimated)	Zoeteman et al., 1980
Soil:	NA	NA

NA = Not available

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Male Charles River rats and female rhesus monkeys excreted a mean of 84 and 40%, respectively, of the radioactivity associated with an oral dose of 10 mg ^{14}C-1,2,4-trichlorobenzene/kg in the urine in 24 hours while fecal elimination accounted for only 11 and 1%, respectively (Lingg et al., 1982). These results indicate that this compound is absorbed from the gastrointestinal tract of these species to at least 89 and 99% of the dose in male rats and female monkeys, respectively.

2.2. INHALATION

As indicated by systemic effects observed in the inhalation toxicity study performed by Kociba et al. (1981), 1,2,4-trichlorobenzene is absorbed by the respiratory tract. This study was not designed to give information on absorption rates; therefore, no further quantitative data are available.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Carlson and Tardiff (1976) observed no effects on weight gain nor consistent alteration in hemoglobin content or packed cell volume in male CD rats (6 animals/group) given 0, 10, 20 or 40 mg/kg/day, 1,2,4-trichlorobenzene by the oral route for 90 days. At 40 mg/kg/day, statistically significant increased ($p<0.05$) liver-to-body weight ratios persisting throughout a 30-day recovery period were observed. Altered liver enzyme activities were observed in all treated groups.

Groups of five female rats (strain not reported) received daily oral doses of 0, 50, 100 or 200 mg 1,2,4-trichlorobenzene/kg/day in corn oil by gavage for 30, 60, 90 or 120 days (Carlson, 1977). After 30 days of exposure, significant increases in liver porphyrins were observed at $\geq$100 mg/kg and in urinary porphyrins at 200 mg/kg. Slight but significant increases were also observed in liver weights at 200 mg/kg. Only liver weights were increased when the compound was administered for 60 days. After 90 days of exposure, slight but significant increases in liver weights at $\geq$50 mg/kg, in liver porphyrins at $\geq$100 mg/kg and in urine porphyrins at 200 mg/kg were observed. A significant increase in liver porphyrins was found after 120 days of exposure at levels $\geq$50 mg/kg. Increased urinary excretion of δ-aminolevulinic acid and porphyrobilinogen was not observed at any dose given for any duration.

Goto et al. (1972) gave male ICR-ICL mice 600 ppm trichlorobenzene (78 mg of compound/kg body weight/day, assuming mice consume the equivalent of 13% of their body weight in food/day) in the diet for 6 months. No effects on body weight, liver, heart and kidney weights were observed. No hepatic or other lesions were observed. The weight gain of treated mice did not differ from controls during the 6-month exposure.

3.1.2. Inhalation. Kociba et al. (1981) exposed 20 male Sprague-Dawley rats, 4 male New Zealand rabbits and 2 male beagle dogs to concentrations of 0, 30 ppm (223 mg/m³) or 100 ppm (742 mg/m³) 1,2,4-trichlorobenzene for urs/day, 5 days/week for a total of 30 exposures in 44 days. No signif-cant treatment-related effects in any of the species tested were observed by gross and comprehensive histological examination. At the 100 ppm level, increased liver weights were observed in dogs and rats. Additionally, increased kidney weights were observed in rats. Rats exposed to 1,2,4-trichlorobenzene at 30 or 100 ppm exhibited increased urinary excretion of porphyrin, which was interpreted as a compound-specific physiological effect rather than a toxic effect. The authors proposed that the urinary porphyrin excretion was the result of P-450 induction rather than a result of alterations in heme destruction or synthesis. This hypothesis was not specifically tested. This interpretation was supported by a follow-up study. The same team of investigators exposed Sprague-Dawley rats of both sexes to 1,2,4-trichlorobenzene at 0, 3 or 10 ppm (0, 22 or 74 mg/m³), 6 hours/day, 5 days/week for 3 months. As reported in an abstract (Watanabe et al., 1978), urinary excretion of porphyrins was slightly increased at 74.2 mg/m³ but returned to control range 2-4 months postexposure. Thus, porphyrin excretion appeared to be the most sensitive indicator of exposure in rats. Exposure to trichlorobenzene at 22.3 mg/m³ did not cause increased porphyrin excretion; therefore, 22.3 mg/m³ was considered a NOEL for rats.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding chronic oral exposure to 1,2,4-trichlorobenzene could not be located in the available literature.

3.2.2. Inhalation. Pertinent chronic inhalation toxicity data could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Kitchin and Ebron (1983) gave oral doses of 0, 36, 120, 360 and 1200 mg/kg/ 1,24-trichlorobenzene dissolved in corn oil to pregnant Sprague-Dawley (CD strain) rats (≥6/group) on days 9-13 of gestation. Mortality increased to 100 and 22% in the 120 and 360 mg/kg/day groups, respectively. Body weight gains were greatly reduced at 360 mg/kg/day. Signs of maternal hepatotoxicity, reflected by a slight and moderate hepatocellular hypertrophy, were observed in 1/9 and 7/8 rats at 120 and 360 mg/kg/day, respectively, but not at 36 mg/kg/day. These histological lesions were not accompanied by changes in maternal liver-to-body weight ratios or hepatic microsomal protein content. 1,2,4-Trichlorobenzene was a strong inducer of hepatic enzymes at 120 and 360 mg/kg/day. Only fetuses in the 0 and 360 mg/kg/day groups were examined for 1,2,4-trichlorobenzene-induced embryonic effects. No statistically significant differences in resorptions, embryolethality or abnormalities were reported; however, 3/12 treated litters exhibited embryolethality as compared with 0/12 in the control litters. Several embryonic parameters were significantly decreased, including embryonic head length, crown-rump length, somite number and total embryo protein content (reduced 23%).

Robinson et al. (1981) gave male and female Charles River rats (each treatment group contained 17-23 litters) 0, 25, 100 or 400 ppm in drinking water in a 3-generation reproductive-teratogenic effect study. The authors estimated that at 83 days of age the F_0 rats had received approximately the following doses: males 2.5, 8.9 and 33 mg/kg/day for the 25, 100 and 400 ppm groups, respectively, and females 3.7, 14.8 and 53.6 mg/kg/day for

the same respective nominal exposure concentrations. At 400 ppm, significantly enlarged adrenals were observed at 95 days of age ($p<0.006$) in both sexes of the F_0 and F_1 generations. There were no effects on fertility, survival, growth, locomotor activity or blood chemistries.

3.3.2. Inhalation. Inhalation data concerning the teratogenicity of 1,2,4-trichlorobenzene were not available.

3.4. TOXICANT INTERACTIONS

Townsend and Carlson (1981) demonstrated that a dose of 181.5 mg/kg (1 mmol/kg) of 1,2,4-trichlorobenzene given to Swiss mice for 7 days protected them from the toxic effects of malathion, malaoxon, parathion and paraoxon.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Human oral carcinogenicity data could not be located in the available literature.

4.1.2. Inhalation. Human inhalation carcinogenicity data could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Oral bioassays could not be located in the available literature.

4.2.2. Inhalation. Inhalation bioassays could not be located in the available literature. The NTP (1986) has not scheduled 1,2,4-trichlorobenzene for carcinogenicity testing.

4.3. OTHER RELEVANT DATA

Yamamoto et al. (1957) applied 0.03 mL/application of a 30 and 60% solution of 1,2,4-trichlorobenzene in acetone to the skin of male and female mice twice weekly for 2 years. Mean survival days were significantly reduced in treated mice of both sexes at 60% and in females at 30%. Nine different tumors were found in the high-dose males as compared with three and eight tumors found in the low-dose and control groups, respectively. The English translation of this Japanese study did not provide sufficient detail of expressed incidence data as the number of animals with tumors/animals examined.

Negative results were obtained in the Salmonella typhimurium reverse mutation assay in strains TA98, TA100, TA1535, TA1537 and TA1538 with or without rat liver S-9 metabolic activation (Schoeny et al., 1979; Lawlor et al., 1979). In general, this test system is insensitive to chlorinated compounds (Rinkus and Legator, 1980).

4.4. WEIGHT OF EVIDENCE

Only qualitative evidence concerning the possible carcinogenic effect of 1,2,4-trichlorobenzene was available. Yamamoto et al. (1957) observed a tumorigenic effect of 1,2,4-trichlorobenzene in a skin-painting test in mice. These data are inadequate for determining carcinogenic risk in humans (U.S. EPA, 1985a). According to the guidelines proposed by EPA for evaluation of carcinogenic potential to humans (U.S. EPA, 1986a), 1,2,4-trichlorobenzene is an EPA Group D - Not Classified and IARC Group 3 chemical, meaning that available data are inadequate for assessment.

5. REGULATORY STANDARDS AND CRITERIA

An ambient water quality criteria for the trichlorobenzenes was not derived by the U.S. EPA (1980a). ACGIH (1986) adopted a ceiling limit of 5 ppm (~40 mg/m³) for 1,2,4-trichlorobenzene. An RfD of 1.4 mg/day for a 70 kg man (0.02 mg/kg/day) has been verified (U.S. EPA, 1986b). This value was obtained by applying an uncertainty factor of 1000 to the NOAEL of 20 mg/kg/day in the Carlson and Tardiff (1976) 90-day study in male CD rats.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). U.S. EPA (1986b) derived an RfD of 1.4 mg/day for a 70 kg man based on an oral subchronic NOAEL of 20 mg/kg/day (Carlson and Tardiff, 1976) (Section 6.2.1.). An uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for intraspecies variation and 10 for the use of subchronic data) was used. An RfD_{SO} of 0.2 mg/kg/day or 14 mg/day is calculated based on the same NOAEL but omitting the factor of 10 for a subchronic study.

6.1.2. Inhalation (RfD_{SI}). In the study by Watanabe et al. (1978), rats were exposed to 0, 3 or 10 ppm (0, 22.3 or 74.2 mg/m³) 1,2,4-trichlorobenzene for 6 hours/day, 5 days/week for 3 months. Increased urinary porphyrin excretion was observed at 74.2 mg/m³ but not at 22.3 mg/m³. Thus, a NOEL of 2.5 mg/kg/day [transformed dose was calculated using exposure data provided by the authors and by assuming an inhalation rate of 0.223 m³/day (U.S. EPA, 1980b) and a body weight of 0.35 kg (U.S. EPA, 1985b) for the rat] was defined (U.S. EPA, 1985a). Kociba et al. (1981) provided further support for this estimate by reporting a rat inhalation LOAEL of 30 ppm (223 mg/m³), 5 days/week for ~6 weeks, based on the same endpoint. An RfD_{SI} is calculated by dividing the NOAEL of 2.5 mg/kg/day by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies variation) to yield 0.025 mg/kg/day or an RfD_{SI} of 1.8 mg/day for a 70 kg man.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). U.S. EPA (1986b) based the RfD for 1,2,4-trichlorobenzene of 1.4 mg/day on a 90-day study by Carlson and Tardiff (1976) in which male CD rats were given oral doses of 0, 10, 20 and 40 mg/kg/day.

Induction of the enzymes of xenobiotic metabolism and increased liver-to-body weight ratio, which persisted for 30 days, was observed at 40 mg/kg/day. Enzyme induction, but not altered liver-to-body weight ratio, was observed at 20 mg/kg/day. Although enzyme induction was a sensitive endpoint, it was not necessarily an adverse effect; therefore, 20 mg/kg/day was considered a NOAEL. This NOAEL was divided by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for intraspecies variation and 10 for a subchronic study) to yield an RfD of 0.02 mg/kg/day or 1.4 mg/day for a 70 kg man. The NOAEL defined in the Carlson and Tardiff (1976) study was supported by a range of values defined in other subchronic studies. NOAELs of 14.8 and 8.9 mg/kg/day for female and male rats, respectively, were reported in the multigeneration reproduction study by Robinson et al. (1981), and a 120-day LOAEL of 50 mg/kg/day based on the endpoint of increased liver porphyrin in rats was observed as well (Carlson, 1977).

An oral CS of 12.4 (Table 6-1) based on a LOAEL defined by a multigeneration reproduction study (Robinson et al., 1981) in which rats exposed to 400 ppm of 1,2,4-trichlorobenzene in drinking water exhibited increased adrenal weight in the first two generations, but not the third, was derived by U.S. EPA (1983a). No effect on adrenal weight was observed at 100 ppm. Doses expressed as mg/kg/day based on water consumption data were provided by the investigators; however, these were not used by U.S. EPA (1983a) to calculate the MED. The preferred approach is to use the experimentally determined values rather than reference values; however, the difference between the resulting MED values is trivial (33.5 and 37.2 mg/day, respectively). The CS of 12.4 calculated by U.S. EPA (1983a) is adopted as the CS for oral exposure to 1,2,4-trichlorobenzene for the purposes of this document.

TABLE 6-1

Composite Scores for the Toxicity of 1,2,4-Trichlorobenzene by Oral/Inhalation Exposure[a]

Species/ Strain	Sex	Exposure Dosage (mg/kg/day)	Human MED (mg/day)[b]	RV_d	Effect	RV_e	CS	Reference
Charles River rats	M,F	31.2[c]	37.2	3.1	increased adrenal weight	4	12.4	Robinson et al., 1981; U.S. EPA, 1983a
Sprague-Dawley rats	M,F	132.0[d]	13.2	3.8	increased uroporphyrin	1	3.8	Watanabe et al., 1978; U.S. EPA, 1983a

[a]Derived in U.S. EPA, 1983a

[b]Uncertainty factor of 10 was applied to approximate chronic exposure

[c]Calculated by multiplying a drinking water concentration of 400 ppm by the fraction of body weight consumed as water/day of 7.8% for the rat (U.S. EPA, 1983a)

[d]Calculated by assuming continuous exposure, an inhalation rate of 20 m^3/day for humans and an absorption factor of 0.5 (U.S. EPA, 1983a,b)

6.2.2. Inhalation (RfD_I). No information concerning the chronic inhalation toxicity of 1,2,4-trichlorobenzene was available; however, the RfD_{SI} of 0.025 mg/kg/day (see Section 6.1.2.) based on a subchronic NOAEL of urinary porphyrin excretion (Watanabe et al., 1978) may be divided by an additional factor of 10 to approximate chronic exposure. This yields an RfD_I of 2.5×10^{-3} mg/kg/day or 0.18 mg/day for a 70 kg man.

U.S. EPA (1983a) derived an inhalation CS (see Table 6-1) for 1,2,4-trichlorobenzene based on an inhalation LOAEL defined by Watanabe et al. (1978). In that study, rats exposed to 10 ppm (74 mg/m³) of 1,2,4-trichlorobenzene, 6 hours/day, 5 days/week for 3 months exhibited a reversible increase in uroporphyrin. No effect on uroporphyrin levels was observed at 22.3 mg/m³ with the same exposure schedule. A few discrepancies between current and previous methodology for deriving a CS were noted. U.S. EPA (1983a) calculated a transformed dose assuming continuous exposure, a human inhalation rate of 20 m³/day and an absorption coefficient of 0.5; the transformed dose was divided by a factor of 10 to expand from subchronic to chronic exposure. Using current methodology, a transformed dose is calculated by assuming continuous exposure, an inhalation rate of 0.223 m³/day for the rat (U.S. EPA, 1980b) and a body weight of 35 kg (U.S. EPA, 1985b). When the transformed dose was divided by 10 for a subchronic study, multiplied by the cubed root of the animal body weight to human body weight ratio and multiplied by 70 kg, a human MED of 10.15 mg/day was obtained, which was substantially similar to the MED of 13.2 mg/day reported in U.S. EPA (1983a). The impact of this discrepancy on the RV_d was minimal, yielding 4.0 by current methodology and 3.8 by previous methodology. U.S. EPA (1983a) assigned an effect ranking of 1 to increased uroporphyrin. The CSs calculated by previous and current methodologies would be 3.8 and 4.1,

respectively. Since this CS is lower than that based on oral exposure, the oral CS of 12.4 is chosen to represent the chronic toxicity of 1,2,4-trichlorobenzene.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The lack of data regarding the carcinogenicity of ingested 1,2,4-trichlorobenzene precluded assessment of carcinogenic risk.

6.3.2. Inhalation. The lack of data regarding the carcinogenicity of 1,2,4-trichlorobenzene by inhalation precluded assessment of carcinogenic risk.

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APPENDIX

Summary Table for 1,2,4-Trichlorobenzene

Route	Species	Experimental Exposure/Dose (mg/kg/day)	Effect	Reference Dose (RfD_S or RfD or CS)	Reference
Inhalation					
RfD_{SI} (formerly AIS)	rats	3 ppm (22 mg/m³), 6 hours/day, 5 days/week for 3 months (2.5)	NOAEL for increased uroporphyrin, observed at 10 ppm	1.8 mg/day	Watanabe et al., 1978
RfD_I (formerly AIC)	rats	3 ppm (22 mg/m³), 6 hours/day, 5 days/week for 3 months (2.5)	NOAEL for increased uroporphyrin, observed at 10 ppm	0.18 mg/day	Watanabe et al., 1978
Oral					
RfD_{SO}	rats	20 (gavage for 90 days)	enzyme induction	14 mg/day	Carlson and Tardiff, 1976
RfD_O	rats	20 (gavage for 90 days)	enzyme induction	1.4 mg/day	Carlson and Tardiff, 1976; U.S. EPA, 1986
Maximum					
CS	rats	400 ppm in drinking water for 90 days (RV_d = 3.1)	increased adrenal weight (RV_e = 4)	CS = 12.4	Robinson et al., 1981; U.S. EPA, 1983a